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An Occurrence of Attractive Alkyl-Phenyl Interaction. The Conformations of Several 1-Phenyl-2-alkanols

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The conformations have been studied, by means of NMR spectroscopy, for a series of 1-alkyl-substituted 2-phenylethyl alcohols with the structure $C_6H_5CH_2CH(OH)$-R, where R$=CH_3$ (**1**), C_2H_5 (**2**), *i*-C_3H_7 (**3**), and *t*-C_4H_9 (**4**). It has been suggested that a rotamer in which the phenyl group is oriented *gauche* to the alkyl (R) and *anti* to the hydroxyl group is most populated in the conformational equilibria of **1**—**3**. Another rotamer (in which Ph is *anti* to R) has, on the other hand, been suggested to be preferred in the conformational equilibrium of **4**. The results have been discussed in the light of the presence of an attractive alkyl-phenyl interaction (CH-π interaction).

In connection with the general interest in the conformational problems of acyclic compounds, we have now studied the conformations of a series of benzylic alcohols with the following structures:

$C_6H_5CH_2CH(OH)$-R
R$=CH_3$ (**1**), C_2H_5 (**2**), *i*-C_3H_7 (**3**),
and *t*-C_4H_9 (**4**).

Results

Tables 1 and 2 list the proton and carbon NMR parameters, respectively, for a series of 1-alkyl-substituted 2-phenylethyl alcohols: 1-phenyl-2-propanol (**1**), 1-phenyl-2-butanol (**2**), 3-methyl-1-phenyl-2-butanol (**3**), 3,3-dimethyl-1-phenyl-2-butanol (**4**). Parts of the ^{1}H NMR spectra are reproduced in Fig. 1.

An inspection of the tables and figures reveals several interesting facts. First, the signal attributed to the OH proton moves progressively to a higher magnetic field as the alkyl group, R, goes from the methyl group through the ethyl and isopropyl groups and then to the *t*-butyl group. The shape of the OH peak is a sharp singlet for **1**, **2**, and **3**; this suggests that the OH group is largely free from the OH-π complexation in these alcohols.1) For the *t*-butyl homologues (**4**), the signals ascribed to the OH and the proton adjacent to this (labeled H_x) are a little bit broader than those in the lower alkyl compounds. Second, the benzylic protons are magnetically nonequivalent, except for **1**, giving rise to a pair of quartets. The spin-coupling constants2) with the vicinal proton (H_x) are larger for the higher part (H_a) of the double quartets than for the lower one (H_b). The coupling constant,

Table 1. Proton chemical shiftsa) and vicinal coupling constantsb) for alcohols, $C_6H_5CH_2CH(OH)$-R

R	Ar	H_a	H_b	H_x	H_y	H_z	OHc)	J_{HaHx}	J_{HbHx}	J_{HyHx}
Me (**1**)	7.17	2.62	2.62	3.87	1.11	—	2.20	6.5	6.5	—
Et (**2**)	7.17	2.57	2.70	3.56	1.41d)	0.93	1.78	7.5	4.5	6.5, 2.0
Pr^i (**3**)	7.17	2.50	2.76	3.45	1.61	0.94e)	1.44	9.0	4.0	6.0
Bu^t (**4**)	7·12	2.37	2.77	3.25f)	—	0.95	1.26f)	10.5	2.5	—

a) Ppm downfield from internal TMS in CCl_4. b) The $^3J_{HH}$'s are the approximate values (in Hz) obtained by the first-order analysis. c) Sensitive to the experimental conditions. d) Almost equivalent for the diastereotopic protons. e) Equivalent for the diastereotopic methyls. f) Broad relative to the respective peak(s) in the lower homologues (see text).

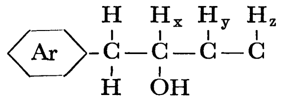
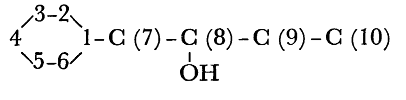


Table 2. Carbon chemical shiftsa) for the alcohols, $C_6H_5CH_2CH(OH)$-R

R	1	2, 6	3, 5	4	7	8	9	10
R	138.6	129.4	128.4	126.4	45.7	68.7	22.7	—
Et	138.7	129.4	128.4	126.3	43.6	74.0	29.5	10.0
Pr^i	139.1	129.3	128.4	126.3	40.7	77.4	33.1	17.4, 18.0
Bu^t	139.9	129.3	128.4	126.1	38.3	80.5	34.7	25.8

a) Ppm downfield from internal TMS in $CDCl_3$.



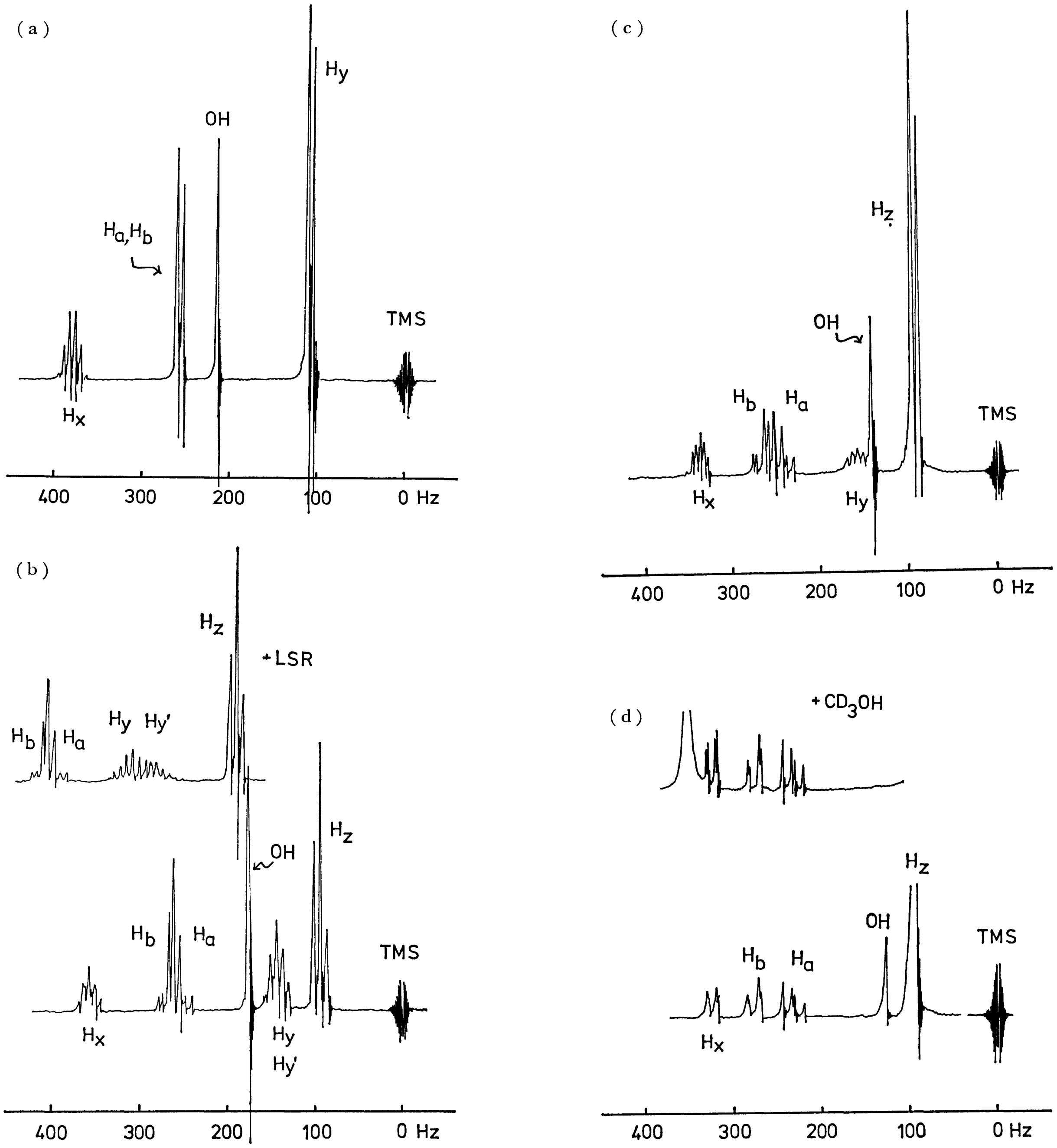


Fig. 1. Proton NMR spectra of (a) 1-phenyl-2-propanol (**1**); (b) 1-phenyl-2-butanol (**2**), insert shows the effect of LSR; (c) 3-methyl-1-phenyl-2-butanol (**3**); and (d) 3,3-dimethyl-1-phenyl-2-butanol (**4**), insert shows the effect of added CD$_3$OH.

$^3J_{\mathrm{HaHx}}$, becomes progressively larger as the methyl group in **1** is replaced by the ethyl, isopropyl, and then *t*-butyl groups; the reverse is true for $^3J_{\mathrm{HbHx}}$. Third, the lanthanoid shift-reagent[3] (LSR) induced shift[4] (LIS, Table 3) is greater for H$_a$ than for H$_b$, the difference in the LIS is most remarkable for **4** (R=Bu^t). The LIS values for the benzylic protons are virtually the same in the cases of **1** and **2**. A signal assignment is possible for the diastereotopic protons if the LIS data are combined with information obtained by the coupling constants. These points will be discussed later.

The conformations of **1**—**4** were then studied by means of a computer simulation[5] of the LIS. Ac-

Table 3. Lanthanoid shift-reagent-induced shifts[a)]
C$_6$H$_5$CH$_2$CH(OH)-R

R		H$_o$	H$_m$	H$_a$	H$_b$	H$_x$	H$_y$	H$_z$
Me	(**1**)	31.7	14.5	61.4	61.4	100	62.1	—
Et	(**2**)	36.7	16.1	64.6	64.6	100	72.7[b)] 61.4	43.6
Pr^i	(**3**)	31.7	11.1	60.0	54.8	100	59.5	38.0[b)] 43.0
Bu^t	(**4**)	29.9	3.7	67.7	40.0	100	—	38.1

a) Relative chemical shifts induced by the addition of Eu(fod)$_3$ to CCl$_4$ solutions. The data are normalized to the value for H$_x$ (LIS$_{\mathrm{rel}}$=100). b) Average values were used in the computations.

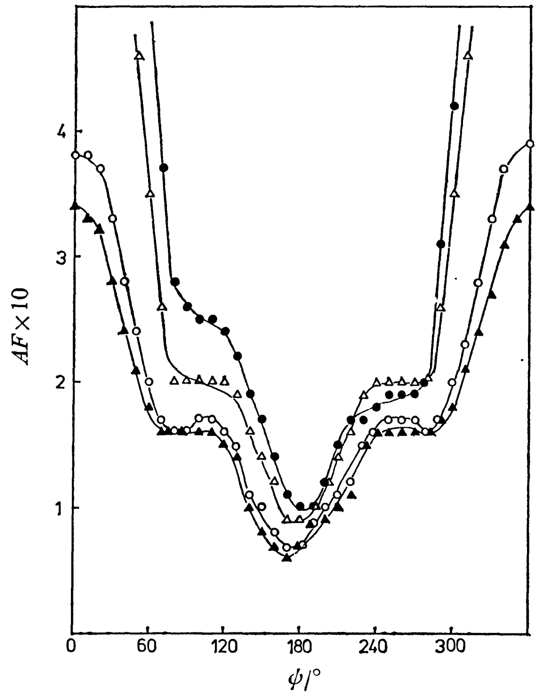


Fig. 2. Plots of AF vs. ϕ for **1**. R is kept constant at 0.32 nm.
●: A=0.0, △: 0.4, ○: 0.8, ▲: 1.2.

cording to the procedure described in an earlier paper,[1b] the positions of the LSR and the geometry of the substrate were varied, step by step, in the search for a reasonable agreement of the computed LIS's with the observed values.[6]

Figure 2 plots the Hamilton reliability factors (AF)[7] against the O–C(8)–C(7)–Ph dihedral angle, ϕ, for a representative case of Compound **1**. Here, the Ln–O distance, R, is fixed at 0.32 nm,[8] while the LSR-distribution index A,[6] is varied from 0.0 to 1.2. A good fit is obtained at ϕ *ca.* 180° in every case. The agreement is worst at ϕ around 0°, but it becomes better with a larger value of A; this is reasonable, since the rotation of the LSR will be hindered if OH (the LSR-complexation site) comes close to the phenyl group. The values of ϕ at the AF-minima do not vary significantly with the change in A; however, the presence of the second (or third) minimum becomes more apparent with a higher value of A.

Figure 3 summarizes the results obtained for **1**, **2**, and **3**. (A and R are fixed at 0.8 and 0.32 nm respectively). A notable feature of these profiles is the presence of three minima in every case. The AF at these ϕ-values are not necessarily good enough to be acceptable, except for the best-fit position. It should be kept in mind that the value of AF represents the plausibility for a single, hypothetical conformation and by no means corresponds to the potential energy or the population of the respective rotamer. However, for reasons previously cited,[1,9] we believe it likely that the appearance of the second and third minima reflects the contribution from other, less populated rotamers. The values of ϕ and AF might thus reflect, though in an indirect manner, the geometry and the relative stability of the respective rotamers.

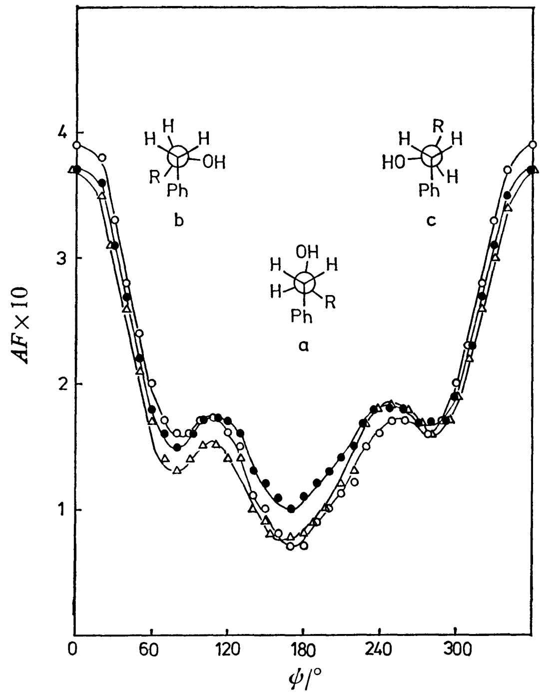
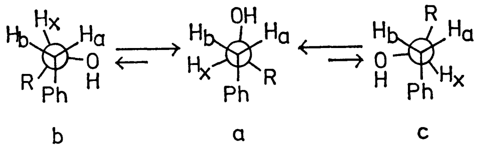


Fig. 3. Plots of AF vs. ϕ for **1**, **2**, and **3**. A and R are kept constant at 0.8 and 0.32 nm respectively. ○: R=Me (**1**), ●: R=Et (**2**), △: R=Pr^i (**3**).



R = Me: a > b ≈ c
Et: a > b ≳ c
Pr^i: a > b > c

Fig. 4. Relative stabilities of the rotamers **a**, **b**, and **c**, suggested for the conformational equilibria of **1**, **2**, and **3**.

An inspection of Fig. 3 suggests that the rotamer with the hydroxyl group *anti* to the phenyl group (ϕ *ca.* 170°, rotamer **a**) is the most populated one in the rotameric mixture of these alcohols. The **b** (ϕ *ca.* 80°) and **c** (ϕ *ca.* 280°) rotamers seem to be of about the same importance for **1** and **2**; the **b** rotamer appears to be more stable than the **c** rotamer in the case of the isopropyl-substituted alcohol (**3**).

A configuration assignment is given in Fig. 4 for the benzylic hydrogens in alcohol **3** (R=Pr^i). With this assignment, the coupling data ($J_{\mathrm{H_aH_x}} > J_{\mathrm{H_bH_x}}$) and the LIS data (larger for H_a) are consistent with the suggested geometries and the equilibrium; a conflict occurs, however, with the alternative assignment. The same conclusion can be reached for **2** and **1**; in the latter case, the chemical shifts of the diastereotopic protons are virtually equivalent.

For the *t*-butyl homologue (**4**), however, a paradoxical result is obtained. With the same signal assignment, the simulation indicates the coexistence of rotamers with ϕ *ca.* 90° and 140° (Figs. 5 and 6a). This conclusion is unacceptable in view of the coupling data (Table 1: 10.5 Hz for H_a and 2.5 Hz for H_b).

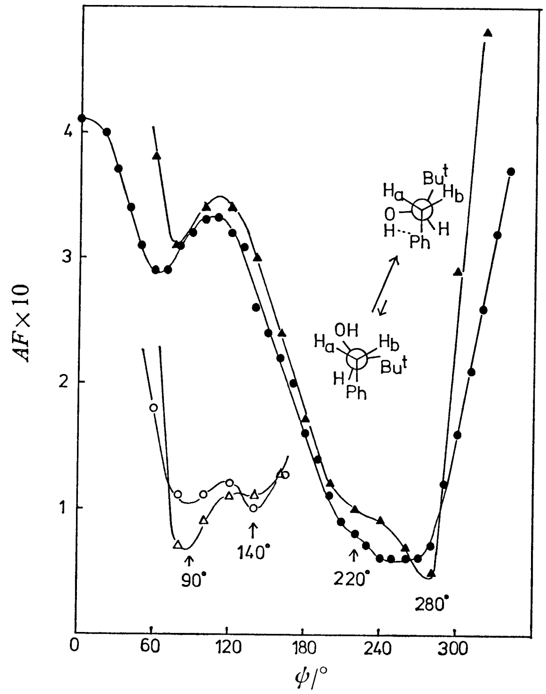


Fig. 5. Plots of AF vs. ψ for **4**. Assignment for the benzylic protons is made as indicated. ▲: A=0.4, ●: A=0.8. Insert shows the profiles obtained with the reversed assignment; this equals to the assignment given for the lower alkyl homologues. △: A=0.4, ○: A=0.8. R is kept constant at 0.32 nm.

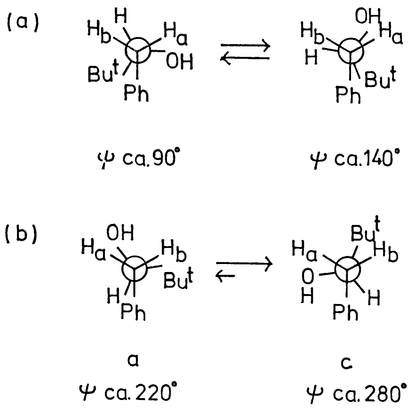


Fig. 6.

A more reasonable conclusion is reached with the alternative assignment. Thus, with an inversed signal assignment, the concomitant presence of rotamers corresponding to the **c** rotamer (ψ *ca.* 280°) and the **a** rotamer (ψ *ca.* 220°) is suggested, the former being likely to be predominant (Figs. 5 and 6b). In this case, the conclusion is compatible with the coupling data.

Support for the above suggestions regarding the rotameric equilibria of **1**—**4** is provided by an inspection of the NMR data. In the **c** rotamer (and **b**), the hydroxyl group is *gauche* to Ph and is expected to participate in the OH-π complexation.(10) The hydroxyl group in the **a** rotamer, in contrast, lies *anti* to the phenyl group. The OH proton in the **c** rotamer can, therefore, be expected to be magnetically more shielded and free from proton exchange, than that in the **a** rotamer.(1) In fact, the hydroxyl proton of **4** gives rise to the highest peak in the series, and it is broader (due to the slow exchange) than that in the lower alkyl homologues. This can be understood by considering the important contribution of the **c** rotamer to **4** and the relative non-importance of this rotamer (and the **b** rotamer) for the other alcohols.

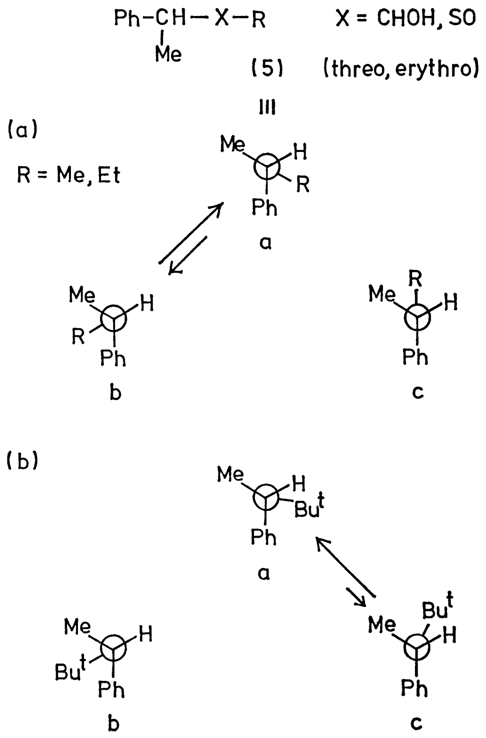


Fig. 7. Rotameric equilibria suggested for the diastereoisomeric pairs of sulfoxides (**5**, X=SO) and alcohols (X=CHOH).

In the **a** rotamer, whereby the OH group is flanked by the two benzylic hydrogens, H_a and H_b, the LIS is anticipated to be about the same for these nuclei. The LIS for H_a and H_b should be very different in the **b** and **c** rotamers, but the effect will be cancelled if these rotamers are populated at an approximately equal concentration. This is what we observed in the proton NMR spectra of **1** and **2**; the trend is reflected in the simulated results. The tendencies observed for the coupling constants as well as the shift data are compatible with the computed results, judging from the assignments given in Figs. 4 and 6b.

Discussion

A remarkable feature of the present result is the finding that the **a** rotamer (Fig. 4) is most populated in the rotameric mixtures of **1**, **2**, and **3**. In the **a** rotamer, the alkyl group lies close to the phenyl group. Note that the benzylic methyl group, which is present in compounds previously studied (Fig. 7), is absent in these molecules. We believe that the above finding can be accommodated only in terms of an attractive force operating between an alkyl and a phenyl group (the CH/π interaction).(1,11)

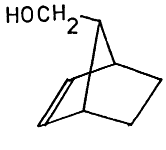
With regard to the *t*-butyl homologue (**4**), the most populated rotamer has been suggested to be the **c** rotamer (Fig. 6b). In this conformation, the *t*-butyl group is oriented *anti* (Bu^t–Ph torsional angle *ca.* 160°) to the phenyl group. The geometry corresponding to the **a** rotamer (Bu^t–Ph torsional angle *ca.* 100°) is found to be the second most stable one in this case. A comment is required on the apparent discrepancy that the **a** rotamer is most stable for **1**, **2**, and **3**, while the **c** rotamer is more important than **a** in the case of **4**. This result is in contrast to the earlier finding that in compounds such as **5** (Fig. 7) the most stable rotamer always has its alkyl group *gauche* to Ph, irrespective of the nature of Groups R and X. The conformational equilibria suggested for sulfoxides (**5**, X=SO)[9a] and alcohols (**5**, X=CHOH)[1b] are illustrated in Fig. 7. In both of these cases, the rotameric mixtures have been shown to consist, principally, of the **a** and **b** rotamers for the lower alkyl homologues and of the **a** and **c** rotamers for the *t*-butyl derivatives, the more stable one being the **a** rotamer in every case.[12] The position of the alkyl group in the most stable geometries has been found to be shifted (slightly, but distinctly) to give a larger R–Ph torsional angle for the *t*-butyl compounds (compare the **a** rotamers in Figs. 7a and 7b) as compared with the lower alkyl homologues.

The conformation of a molecule is, indeed, a consequence of a compromise of a number of interactions. In compounds such as **5**, where a methyl group is present in the benzylic position, the geometry of a molecule is controlled, primarily, by the balance of two interactions: R *vs.* $\mathrm{CH_3}$, and R *vs.* Ph. These interactions may be attractive at an appropriate distance (the dispersion force[13] and/or the CH–π interaction[11]) or repulsive if the relevant groups come too close.

The suggestion that the **c** rotamer (ϕ *ca.* 280°) represents the most stable conformation for **4** is understood in view of the absence of the benzylic methyl; the **a** rotamer might have become energetically less favorable than **c** in the present molecular environment. The **a** rotamer may be destabilized by the unfavorable (repulsive van der Waals) interaction between Bu^t and a benzylic hydrogen ($\mathrm{H_b}$). This situation might occur when a methyl group in Bu^t takes a suitable position for the CH–π bonding.

Other possible factors which may contribute to controlling the rotameric equilibria of these compounds are the OH–π hydrogen bonding and the O–Ph dipole-quadrupole and *gauche*-vicinal H–H interactions. Some speculations will be made, on the basis of the suggested geometries of the preferred conformations, as to the factors influencing the molecular geometries of these alcohols.

The operation of the attractive CH–π interaction is possible in both the **a** and **b** rotamers (Fig. 4). However, the **a** rotamer has been found to be more stable than **b** in all cases. To accommodate this, it may be pointed out that there are two vicinal H–H interactions in the **b** rotamer. According to Wertz and Allinger, this interaction is very destabilizing.[14] The O–Ph dipole-quadrupole interaction[15] may also destabilize the **b** rotamer (and **c**).[16] The OH–π interaction[10,17] is undoubtedly attractive, but the other unfavorable interactions might override its effect. In this respect, it should be noted that OH–π bonding has not been observed in such compounds as **6** and **7**[18] even though these molecules appear to be ideally constituted for such interactions to take place. The observance of the OH–π hydrogen bonding might, therefore, be merely a consequence of a given (somewhat compelled) geometry of a molecule.



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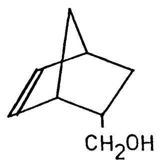

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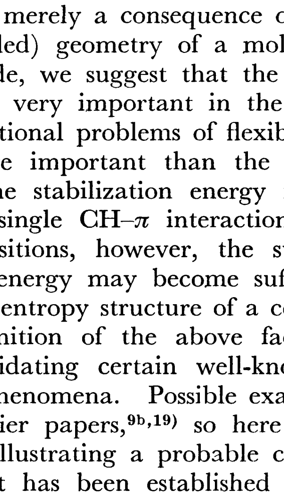
To conclude, we suggest that the attractive CH–π interaction is very important in the consideration of the conformational problems of flexible molecules. It may be more important than the OH–π hydrogen bonding. The stabilization energy is probably very small for a single CH–π interaction. In some molecular dispositions, however, the sum total of the stabilization energy may become sufficiently large to ensure a low-entropy structure of a complex molecule.

The recognition of the above facts would be of help in elucidating certain well-known, but poorly understood phenomena. Possible examples have been given in earlier papers,[9b,19] so here we will confine ourselves to illustrating a probable case from terpene chemistry. It has been established that levopimaric acid (**8**) exists in a folded conformation.[20,21] It is also well known that a considerable fraction of the folded conformer (with an axially oriented isopropyl group) contributes to conformational equilibrium of α-phellandrene (**9**).[20,22] These results were once attributed, by Burgstahler *et al.*[20] to the presence of some type of attractive interaction which stabilizes an otherwise unfavorable conformation. The above interpretation was later replaced by alternative ones based principally on repulsive steric effects.[21,23]



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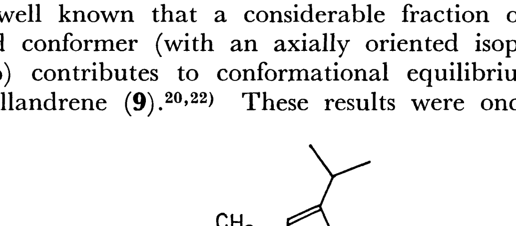

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The well-known diene chirality rule, in its original form,[24] states that the long wavelength $\pi\rightarrow\pi^*$-transition Cotton effect is mainly controlled by the helicity and the amount of twist of a conjugated diene. Re-

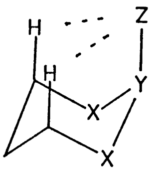

Fig. 8. A possible explanation (in terms of the CH–π or CH–n[9b] interactions) for the axial preference of the Group Z.
Z: unsaturated groups or hetero atoms. X: O, S, CH_2 *etc.* Y: CH, S, or P.

cently, Burgstahler and his associates presented evidence[25] that the Cotton effects of 1,3-cyclohexadienes are primarily determined by the chirality contributions of allylic axial substituents according to the size or polarizability of the group. The suggestion has gained rapid acceptance and has been followed by quantum mechanical studies[26] and the proposal of an empirical quadrant rule.[27] In particular, Rosenfield and Charney presented evidence,[26a] obtained by MO calculations, that an axially oriented allylic hydrogen and methyl group contribute significantly to the rotatory strength of cisoid diene, a methyl group being *ca.* twice as effective as a hydrogen atom.

We suggest that these results are better accommodated in terms of the CH–π interaction. In our view, the folded conformations of **8** and **9** are consequences of an attractive interaction.[28] Also, it seems reasonable to suggest that the axial allylic (or homoallylic[29]) effect[25] operates mainly through the dissymmetric perturbation of the π^* orbital of the chromophore by virtue of the C–H groups,[30] which are oriented suitably for this interaction to take place. Inspections of Dreiding models suggest, in fact, that such an interaction is possible between CH groups and conjugated π-systems whenever a significant contribution of axial allylic or homoallylic (or even remoter) groups is present.[25,27,29] The same kind of argument will perhaps apply to the theoretical background, at least in part, of the Octant rules of ketones[31] and olefins,[32] and to the genesis of the 2-axial ketone effect.[33] Also noteworthy in this regard is the tendency for a group which bears π- or unshared-electrons to adopt the axial conformation (configuration) in saturated six-membered heterocycles (Fig. 8).[34] It is tempting to speculate about the possibility that the above effect (the generalized anomeric effect) is ascribable, at least in part, to the CH–π (and CH–n[9b]) interaction.[35]

Experimental

Materials. The alcohols (**1**—**4**) were prepared by treating phenylacetaldehyde with an appropriate Grignard reagent, RMgCl. The samples were purified as usual and shown gas-chromatographically to be pure.

NMR Spectra. ^1H NMR spectra were recorded at 30 °C on a JEOL MH-100 spectrometer (100 MHz) for *ca.* 0.2 M solutions in CCl_4 (locked to internal TMS; sweep-rate, $4\ Hz\ s^{-1}$). The calibrations of the chemical shifts (reported in ppm relative to internal TMS) were made by referring to the signals of standard samples. The coupling constants were determined by an inspection of the spectra and are accurate to ± 0.5 Hz. The ^{13}C NMR spectra were obtained at 27 °C on a JEOL FX-100 instrument (25.05 MHz) for $CDCl_3$ solutions in 10 mm ϕ-sample tubes (FT-conditions: data points, 8 K; spectral width, 4 kHz; flip angle, 45°; repetition time, 1.2 s). The signal assignments were made by the use of selective and gated decoupling techniques. The chemical shifts are reported in ppm downfield from internal TMS ($\delta=0$) and are accurate to ± 0.04 ppm.

LIS Measurements. Weighted LSR [$Eu(fod)_3$] was added, step by step, to a solution containing a known amount of a substrate, and the signals were followed in the spectra. A least-squares fit of the experimental points was used to obtain the observed LIS's used in the computations. In all cases straight lines were obtained with correlation coefficients of $r>0.998$.

We wish to thank Professor Naoya Nakagawa (The University of Electro-communications) for his useful discussions, and Drs. Teiichiro Ito and Koshiro Umemura (Meiji Seika Kaisha) for their encouragement.

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7) $AF=[\sum_i(\mathrm{LIS}_i^{\mathrm{obsd}}-\mathrm{LIS}_i^{\mathrm{calcd}})^2/\sum_i(\mathrm{LIS}_i^{\mathrm{obsd}})^2]^{1/2}$. The calculated shifts were normalized to the average experimental LIS in the computational process.

8) The reasonable fit has invariably been found at about this value.

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